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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/829,968	04/11/2001	Klaus Peter Hirth	038602/1140	1137

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EXAMINER
HUNT, JENNIFER ELIZABETH

ART UNIT	PAPER NUMBER
1642	3

DATE MAILED: 03/20/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/829,968	HIRTH, KLAUS PETER	
	Examiner	Art Unit	
	Jennifer E Hunt	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 20-25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 20-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Acknowledgement is made of applicant's cancellation of claims 1-19, and addition of new claims 21-25. Claims 20-25 are pending in the application and considered herein.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 24 and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The limitation of co-localization of VEGF with tyrosine kinase inhibitors, specifically KDR/flk-1 receptor, the flt-1 receptor, and/or the tek/tie-2 receptor has been added, but is not supported by the original specification. The specification does not disclose co-localization of VEGF and the instant receptors, or that this co-localization would be useful for a method of determining metastasis.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toi et al., Breast Cancer Research and Treatment, Vol 36, pages 193-204, September 1, 1995, Battegay, Journal of Molecular Medicine, Vol 73, 1995, Rockwell et al., US Patent 5,840,301, issued November 24, 1998, or Janjic et al., US Patent 5,849,479, issues December 15, 1998, in view of Hanna, Jr. et al. US Patent 5,474,755, issued December 12, 1995, or De Jager et al., Seminars in Nuclear Medicine, Vol XXIII, No. 2, pages 165-179, April 1993.

Toi et al. teaches that VEGF is a reliable measure of micro vascularization and that micro vascularization is indicative of metastasis.(page 197, second paragraph, page 198, last paragraph, page 201, 2nd column, first paragraph, and page 202, first column) Further, Toi et al. teaches use of imaging to detect change in angiogenic phenotype to diagnose cancer. Toi et al. also teaches VEGF detection using PCR and antibodies. (Page 202)

Battegay teaches that VEGF expression is indicative of a change to angiogenic phenotype. Battegay further teaches that increased or abnormal secretion of VEGF is indicative of tumor growth and angiogenesis, which corresponds to metastasis, and that in vivo assays are useful for detecting metastasis. (Page 334, second column, third paragraph, Page 340, second column, third paragraph and page 335, first column, first paragraph). Battegay also teaches that the VEGF receptors flt-1 and flk-

1 are expressed in proliferating and invading cells of a malignant tumor and that they interact directly with VEGF, thus would be located in the same or similar locations if they were active. (page 336, second column, second paragraph)

Rockwell et al. teaches an in vivo method of detection of VEGF and it's receptors, including flt-1 and flk-1, including labeled antibodies, and that VEGF is indicative of angiogenesis and tumor proliferation and growth. Rockwell et al. also teaches that up regulation of VEGF and receptors is in proximity to the tumor. (columns 1,2, and 7).

Janjic et al. teaches that angiogenesis accompanies metastasis, and that VEGF induces angiogenesis in vivo. Additionally, VEGF acts by direct association with its receptors, including flt-1 and kdr/flk-1. Janjic et al. specifically teaches that expression of VEGF and its receptors is associated with tumor growth, which would include metastasis at a site distal from a primary tumor. (Columns 1 and 2)

Thus, Toi et al., Battegay, Rockwell et al., and Janjic et al. collectively teach that VEGF expression is a reliable marker of angiogenesis, which is a prerequisite for metastasis. They teach that detection of angiogenesis reliably predicts metastasis. They also teach that VEGF receptors, including KDR/flk-1 and flt-1 are co-expressed with VEGF and that all are detectable and useful in assays, including in vivo assays and assays which use antibodies, for angiogenic transformation and progression. Toi et al., Battegay, Rockwell et al., and Janjic et al. fail to teach the specific method of in vivo diagnosis of distal metastasis using VEGF and receptor localization, including a VEGF receptor protein, X-Ray, CAT-Scan, or MRI.

Detection of metastasis using antibodies or receptors to localize a known cancer antigen, including X-Ray, CAT-Scan, or MRI is well known in the art, as taught, for example by Hanna, Jr. et al., or De Jager et al.

Hanna, Jr. et al. teaches that antibodies which bind cancer antigens can be used in combination with CAT-scans to diagnose metastasis (column 2, lines 44-54, and column 8, line 62- column 9, line 26.)

De Jager et al. teaches that antibodies which bind cancer antigens can be used in combination with CAT-scans to diagnose metastasis (see abstract and entire document.)

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to use the known methods and materials of tumor and metastasis detection using localization, including the in vivo detection techniques such as CAT-scan exemplified in Hanna Jr. et al, or De Jager et al. with the antibodies or receptor proteins to the known metastatic indicator VEGF and it's receptors taught in Toi et al., Battegay, Rockwell et al., and Janjic et al. and one would have been motivated to do so because VEGF and it's receptors are useful for detecting metastasis, as taught by Toi et al., Battegay, Rockwell et al., and Janjic et al.

6. Claims 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boocock et al., Journal of the National Cancer Institute, Vol. 87, No. 7, April 5 1995, pages 506-516, or Warren et al., Journal of Clinical Investigations, Vol. 95, April 1995,

pages 1789-1797, or Halva et al., American Journal of Pathology, Vol. 146, No. 2, February 1995, pages 368-378, in view of Hanna, Jr. et al. US Patent 5,474,755, issued December 12, 1995, or De Jager et al., Seminars in Nuclear Medicine, Vol XXIII, No. 2, pages 165-179, April 1993.

Boocock et al. teaches a method of detecting metastasis by administering a detectably labeled ligand which specifically recognizes VEGF, KDR, and flt (see abstract, page 511, and page 513, column 1)

Warren et al., teaches a method of detecting metastasis by administering a detectably labeled ligand which specifically recognizes VEGF (see abstract, page 1791, second column, and figures 2a and 2b, and 1793-1794)

Halva et al., teaches a method of detecting metastasis by administering a detectably labeled ligand which specifically recognizes VEGF, KDR, FLT1, and/or Tie (see abstract, and table 3)

Boocock et al., Warren et al., and Halva et al. fail to teach the specific method of in vivo diagnosis of distal metastasis using VEGF and receptor localization, including a VEGF receptor protein, X-Ray, CAT-Scan, or MRI.

Detection of metastasis using antibodies or receptors to localize a known cancer antigen, including X-Ray, CAT-Scan, or MRI is well known in the art, as taught, for example by Hanna, Jr. et al., or De Jager et al.

Hanna, Jr. et al. teaches that antibodies which bind cancer antigens can be used in combination with CAT-scans to diagnose metastasis (column 2, lines 44-54, and column 8, line 62- column 9, line 26.)

De Jager et al. teaches that antibodies which bind cancer antigens can be used in combination with CAT-scans to diagnose metastasis (see abstract and entire document.)

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time of applicant's invention to use the known methods and materials of tumor and metastasis detection using localization, including the in vivo detection techniques such as CAT-scan exemplified in Hanna Jr. et al, or De Jager et al. with the antibodies or receptor proteins to the known metastatic indicator VEGF and it's receptors taught in Boocock et al., Warren et al., and Halva et al. and one would have been motivated to do so because VEGF and it's receptors are useful for detecting metastasis, as taught by Boocock et al., Warren et al., and Halva et al.

7. Claims 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toi et al., Breast Cancer Research and Treatment, Vol 36, pages 193-204, September 1, 1995, or Battegay, Journal of Molecular Medicine, Vol 73, pages 333-346, 1995, or Rockwell et al., US Patent 5,840,301, issued November 24, 1998, or Janjic et al., US Patent 5,849,479, issues December 15, 1998, or Boocock et al., Journal of the National Cancer Institute, Vol. 87, No. 7, April 5 1995, pages 506-516, or Warren et al., Journal of Clinical Investigations, Vol. 95, April 1995, pages 1789-1797, or Halva et al., American Journal of Pathology, Vol. 146, No. 2, February 1995, pages 368-378, in view of Hanna, Jr. et al. US Patent 5,474,755, issued December 12, 1995, or De

Jager et al., Seminars in Nuclear Medicine, Vol XXIII, No. 2, pages 165-179, April 1993, and further in view of Kendall et al. Proceedings of the National Academy of Science, Vol 90, pages 10705-10709, (1993).

Toi et al., Battegay, Rockwell et al., Janjic et al., Boocock et al., Warren et al., or Halva et al., and Hanna, Jr. et al., or De Jager et al. teach as applied to claims 20-21 and 23-25 supra, and that protein conjugates can be used to detect cancer receptors *in vivo*.

Toi et al., Battegay, Rockwell et al., Janjic et al., Boocock et al., Warren et al., or Halva et al., and Hanna, Jr. et al., or De Jager et al. fail to teach detecting the presence of VEGF using a VEGF receptor fusion protein or a VEGF receptor conjugated protein.

Kendall et al. teaches that VEGF receptor conjugated proteins, including FLT can be used to bind to and detect or inhibit VEGF (see page 10705 and abstract).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to combine the *in vivo* methods of detecting metastasis using VEGF taught by Toi et al., Battegay, Rockwell et al., Janjic et al., Boocock et al., Warren et al., or Halva et al., and Hanna, Jr. et al., or De Jager et al., by using a VEGF receptor fusion protein or a VEGF receptor conjugated protein, as taught by Kendall et al., and one would have been motivated to do so because VEGF receptor proteins bind tightly to VEGF *in vivo* as taught by Kendall et al., and thus would be effective for detecting VEGF.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E Hunt whose telephone number is (703) 308-7548. The examiner can normally be reached on Monday-Friday, 6-3:30. .

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

Jennifer E Hunt
Examiner
Art Unit 1642

jeh
March 17, 2002

Sheela J. Huff
SHEELA HUFF
PRIMARY EXAMINER